ONCOLYTIC VIRUSES THAT EXPRESS MULTI-SPECIFIC IMMUNE CELL ENGAGERS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/913,655, filed October 10, 2019, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] This disclosure relates to myxoma viruses and their uses for treatment of cancers, for example, treatment of hematological cancers with a myxoma virus that expresses one or more multi-specific immune cell engagers.

BACKGROUND

[0003] Current treatments used to treat various types of cancer tend to work by poisoning or killing the cancerous cell. Unfortunately, treatments that are toxic to cancer cells typically tend to be toxic to healthy cells as well. Moreover, effective treatments for cancer remain elusive. Current mainstream therapies such as chemotherapy and radiotherapy can have a narrow therapeutic window (e.g., a concentration high enough to achieve efficacy but low enough to avoid toxicity). These types of therapies are considered blunt tools that have limited applicability due to the varying types of tumor cells and the limited window in which these treatments can be administered.

SUMMARY

[0004] Disclosed herein, in ~~some~~ one aspect~~s~~, is a myxoma virus (MYXV) comprising a transgene that encodes a multi-specific immune cell engager.

[0005] In some ~~embodiments~~examples, the multi-specific immune cell engager comprises a Bi-specific Natural Killer and Neutrophil engager (BiKE), a Bi-specific T Cell Engager (BiTE), or a membrane-integrated T cell engager (MiTE). In some ~~embodiments~~examples, the multi-specific immune cell engager binds to an antigen present on a hematologic cancer cell. In some ~~embodiments~~examples, the hematologic cancer cell is a myeloma cell, a leukemia cell, or a lymphoma cell. In some ~~embodiments~~examples, the BiKE binds to an antigen present on a natural killer cell or a neutrophil. In some ~~embodiments~~examples, the BiTE binds to an antigen present on a T cell. In some ~~embodiments~~examples, the MiTE binds to an antigen present on a T cell. In some

~~embodiments~~examples, the BiKE binds to CD16 or CD138. In some ~~embodiments~~examples, the BiKE binds to CD16 and CD138. In some ~~embodiments~~examples, the BiTE binds to CD3 or CD138. In some ~~embodiments~~examples, the BiTE binds to CD3 and CD138. In some ~~embodiments~~examples, the MiTE binds to CD3 or CD138. In some ~~embodiments~~examples, MiTE binds to CD3 and CD138. In some ~~embodiments~~examples, the multi-specific immune cell engager comprises one or more single chain variable fragments (scFvs) derived from an anti-human CD antibody. In some ~~embodiments~~examples, the multi-specific immune cell engager comprises one or more humanized single chain variable fragments (scFvs). In some ~~embodiments~~examples, the BiKE comprises a sequence that is at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identical to any one of SEQ ID NOs: 4-21. In some ~~embodiments~~examples, the BiTE comprises a sequence that is at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identical to any one of SEQ ID NOs: 6, 7, 10-15, or 32-39. In some ~~embodiments~~examples, the MiTE comprises a sequence that is at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% identical to any one of SEQ ID NOs: 6, 7, 10-15, or 32-39. In some ~~embodiments~~examples, the transgene is located between the M135 gene and M136 gene of the genome of the MYXV. In some ~~embodiments~~examples, the MYXV further comprises a reporter gene. In some ~~embodiments~~examples, the reporter gene encodes a fluorescent protein. In some ~~embodiments~~examples, the reporter gene encodes a luminescent substrate or an enzyme. In some ~~embodiments~~examples, the MYXV further comprises a mutation in the genome of the MYXV. In some ~~embodiments~~examples, the mutation is present in one or more genes selected from the group consisting of M001R, M002R, M003.1R, M003.2R, M004.1R, M004R, M005R, M006R, M007R, M008.1R, M008R, M009L, M013, M036L, M063L, M11L, M128L, M131R, M135R, M136R, M141R, M148R, M151R, M152R, M153R, M154L, M156R, M-T2, M-T4, M-T5, M-T7, and SOD. In some ~~embodiments~~examples, the mutation is a deletion. In some ~~embodiments~~examples, the deletion deletes at least a portion of M135R. In some ~~embodiments~~examples, the MYXV is present in a composition that comprises the MYXV and a pharmaceutically acceptable carrier. In some ~~embodiments~~examples, the MYXV or the composition is administered to a subject in need thereof in a method of treating a hematological cancer. In some ~~embodiments~~examples, the subject is a human. In some ~~embodiments~~examples, the MYXV is capable of infecting cells that have a deficient innate anti-viral response. In some ~~embodiments~~examples, the MYXV is capable of infecting cancer cells. In some ~~embodiments~~examples, the hematological cancer is a myeloma, multiple myeloma, leukemia, or lymphoma. In some ~~embodiments~~examples, the MYXV is administered to the subject with a leukocyte in a method for treating cancer, wherein the leukocyte comprises or is associated with the MYXV. In

some ~~embodiments~~examples, the method further comprises adsorbing the MYXV *ex vivo* onto a surface of the leukocyte. In some ~~embodiments~~examples, the adsorbing the MYXV onto the surface of the leukocyte comprises exposing the leukocyte to the myxoma virus under conditions that permit binding of the myxoma virus to the surface of the leukocyte. In some ~~embodiments~~examples, the adsorbing comprises exposing the leukocyte to the MYXV for at least five minutes. In some ~~embodiments~~examples, adsorbing comprises exposing the leukocyte to the MYXV for about one hour. In some ~~embodiments~~examples, the adsorbing comprises exposing the leukocyte to the MYXV at a multiplicity of infection (MOI) of between about 0.001 and 1000. In some ~~embodiments~~examples, the adsorbing comprises exposing the leukocyte to the MYXV at a multiplicity of infection (MOI) of between about 0.1 and 10. In some ~~embodiments~~examples, the leukocyte is obtained from peripheral blood. In some ~~embodiments~~examples, the leukocyte is obtained from bone marrow. In some ~~embodiments~~examples, the leukocyte is a peripheral blood mononuclear cell. In some ~~embodiments~~examples, the leukocyte is obtained from the subject's tissue. In some ~~embodiments~~examples, the leukocyte is obtained from a donor's tissue that is HLA-matched, HLA-mismatched, haploidentical, or a combination thereof relative to the subject. In some ~~embodiments~~examples, the leukocyte is formulated in a pharmaceutical composition. In some ~~embodiments~~examples, the leukocyte is administered systemically. In some ~~embodiments~~examples, the leukocyte is administered parenterally. In some ~~embodiments~~examples, the leukocyte is administered intravenously.

[0006] Some ~~embodiments~~examples relate to a myxoma virus (MYXV) comprising a transgene that encodes a multi-specific immune cell engager.

[0007] Some ~~embodiments~~examples relate to a composition comprising the myxoma virus described herein and a pharmaceutically acceptable carrier.

[0008] Some ~~embodiments~~examples relate to a method of treating a hematological cancer in a subject in need thereof, comprising administering to the subject the myxoma virus described herein.

[0009] Some ~~embodiments~~examples relate to a method of treating a hematological cancer in a subject in need thereof, comprising administering to the subject a leukocyte, wherein the leukocyte comprises the myxoma virus described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The novel features of certain embodiments of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which: